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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/720,431	11/24/2003	Takuji Shirasawa	2352.001	5106

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/720,431	SHIRASAWA ET AL.	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Restriction of Invention

Applicant's response to Restriction and/or election of Species requirements of 10/13/2005 is acknowledged. Applicants elected without traverse Group I (i.e., claims 1-12) (as directed to part (i) of claims 1-3, 5, 7, 9, and 11). The Applicant's Response was filed on 12/13/ 2005.

Claims 1-13 are pending and Claims 1-12 as specified above are under examination.

Specification

Applicants claim to priority date of 03/06/2003 is denied because of the failure to provide a certified copy of the foreign document. Priority date accorded is 11/24/2003, the filing date of the instant application.

Specification is objected to because of the failure of the applicant to provide the priority date claims and continuation data on the first paragraph of the specification.

Claim Objections

Claim 7 objected to because of the following informalities: the phrase '...modificating of a tissue..' is undefined. For the examination purpose the phrase is read as '....modification of a tissue...'. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 12 are rejected under 102(b) as being anticipated by Hoffman et al., (Patent No. US 5,028,588). The above claims are directed to a pharmaceutical composition for alleviating hypoxia, comprising α-globin having the Titusville mutation.

Hoffman teaches pharmaceutical compositions of mutant hemoglobins that are useful as substitutes for red blood cells in delivery of oxygen to tissues (see entire document) and a need for mutant hemoglobins with reduced affinity for oxygen (low oxygen affinity state; 'right-shifted') or increased P50, the partial pressure at which the oxygen-carrying solution is half saturated with oxygen, for efficient unloading of bound oxygen in tissues in need of O_2, a limitation observed with native hemoglobin, when used as a blood substitute (col. 1-2). Hoffman further teaches that one can use either certain naturally occurring mutants in α or β chain of the hemoglobin or use non-naturally occurring low affinity hemoglobin mutants (col.3-5, col.21-22 and table 1; col24, Table 2, col.27-28). He further **points out specifically a natural mutant where in Asp94Asn of α-globin (Titusville mutation**) as one of the preferred candidates that can used in the composition (col.7, lines 50-59, and teaches methods of making recombinant globin proteins (col.14-18) for mass production of compositions as blood substitutes (pharmaceutical composition). Thus the rejected claims are within the scope of the Hoffman's, disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-4 are rejected under 35 USC 103 (a) as being unpatentable over Hoffman et al., (Patent No. US 5,028,588) as applied to claim 1 and 12 above in view of Standl et al (2001, Expert. Opin. Biol. Ther. 1:831-843) and further in view of Baron et al (1999, Critical Care 3:R99-R102).

The above claims are directed to a pharmaceutical composition for alleviating hypoxia and ischemia, comprising administering α-globin having the Titusville mutation.

Hoffman teaches pharmaceutical compositions of mutant hemoglobins that are useful as substitutes for red blood cells in delivery of oxygen to tissues (see entire document) and a need for mutant hemoglobins with reduced affinity for oxygen (low oxygen affinity state; 'right-shifted') or increased P50, the partial pressure at which the oxygen-carrying solution is half saturated with oxygen, for efficient unloading of bound oxygen in tissues in need of O_2, a limitation observed with native hemoglobin, when used as a blood substitute (col. 1-2). Hoffman further teaches that one can use either certain naturally occurring mutants in α or β chain of the hemoglobin or use non-naturally occurring low affinity hemoglobin mutants (col.3-5, col.21-22 and table 1; col24, Table 2, col.27-28). He further **points out specifically a natural mutant where in Asp94Asn of α-globin (Titusville mutation**) as one of the preferred candidates that can used in the composition (col.7, lines 50-59, and teaches methods of making recombinant globin proteins (col.14-18) for mass production of compositions as blood substitutes (pharmaceutical composition). However, Hoffman does not teach explicitly different clinical conditions such as ischemia, under which the compositions are administered as blood substitutes to a subject.

Standl teaches in a review of the use of hemoglobin based oxygen carriers (HBOCs) including genetically modified or recombinant hemoglobins produced by various methods (see for example p.831, abstract; p.833, col.2, 4th paragraph) and their superiority over other blood substitutes such ahs cross linked hemoglobins etc and their progress to Phase III clinical trials. **HBOC with a higher than normal p50** (low oxygen affinity state; e.g., Titusville mutant of instant application) possess an enhanced potential of oxygen release to the tissues and be able to provide enhanced oxygen supply for the tissues (p.835, col.1, 2nd paragraph). More recent investigations have

shown that HBOC are not only simple erythrocyte transfusion substitutes but are **highly effective oxygen donators in terms of tissue oxygenation** (p.839, 2nd paragraph). "HBOC open the door for a new therapeutic strategy: plasmatic oxygen delivery with physiological concentrations of inspired oxygen. In specific situations (e.g., **ischemia** or arterial stenosis). HBOC have advantages over red blood cells because **they can reach post-stenotic or poorly perfused tissues (i.e.,hypoxia)with the plasma stream, where erythrocytes are not able to pass**. In addition to significant plasmatic oxygen transport, HBOC also enhance tissue oxygenation because of the facilitated oxygen release by HBOC and from remaining erythrocytes (p. 831, abstract).

Baron et al teaches several hemoglobin based therapeutics now in clinical trials including engineered recombinant alpha subunits (p.R100, col.1, 3rd paragraph). Further he teaches that such hemoglobin therapeutics could provide an immediate on-site replacement for traumatic blood loss and in **therapy to prevent global ischemia and organ failure or treat focal ischemia** (R.102, col.1, 2nd paragraph). The latter two conditions of ischemia of Baron read broadly on the art encompasses all the limitations of instant claim on ischemic conditions including respiratory failure, ischemic diseases, ischemic heart diseases, myocardial infraction, angina, cerebral ischemia, obstructive arterial disorders, or obstructive arteriosclerosis.

Thus it would have been obvious for one of ordinary skill in the art to incorporate the compositions of Titusville mutant hemoglobin for the methods of treating ischemic condition or to enhance to oxygen perfusion of tissues of a subject in need. One of ordinary skill in the art would have been motivated to employ the erythrocyte free hemoglobin compositions with Titusville mutation in alpha subunit as it enhances tissue oxygenation with out the risk of allogenic reactions or infections observed with whole blood or erythrocyte transfusions as well the easy flow across the arterial blocks (that block erythrocytes) generally observed during ischemia. One of ordinary skill in the art would have reasonable expectation of success in making and using blood transfusion substitutes of pharmaceutical compositions comprising alpha globins with Titusville mutation for ischemia therapy and for enhancing oxygen perfusion tissues experiencing

hypoxia because of the teachings of Hoffman and Standl and Baron as above. Thus, the claimed invention was *prima facie* obvious.

Claims 5-10 are rejected under 35 USC 103 (a) as being unpatentable over Hoffman et al., (Patent No. US 5,028,588) as applied to claim 1 and 12 above in view of Li et al (2000, Nature Medicine 6:1115-1120)

The above claims are directed to a pharmaceutical composition for enhancing oxygen metabolism, exercise capacity and for modification of tissue, comprising administering α-globin having the Titusville mutation.

Hoffman teaches pharmaceutical compositions of mutant hemoglobins that are useful as substitutes for red blood cells in delivery of oxygen to tissues (see entire document) and a need for mutant hemoglobins with reduced affinity for oxygen (low oxygen affinity state; 'right-shifted') or increased P50, the partial pressure at which the oxygen-carrying solution is half saturated with oxygen, for efficient unloading of bound oxygen in tissues in need of O_2, a limitation observed with native hemoglobin, when used as a blood substitute (col. 1-2). Hoffman further teaches that one can use either certain naturally occurring mutants in α or β chain of the hemoglobin or use non-naturally occurring low affinity hemoglobin mutants (col.3-5, col.21-22 and table 1; col24, Table 2, col.27-28). He further **points out specifically a natural mutant where in Asp94Asn of α-globin (Titusville mutation**) as one of the preferred candidates that is used in the composition (col.7, lines 50-59, and teaches methods of making recombinant globin proteins (col.14-18) for mass production of compositions as blood substitutes (pharmaceutical composition). However Hoffman does not teach the limitation of enhancing oxygen metabolism, exercise capacity or modification of tissues and exercise capacity.

Li teaches mutant Ucp-H&L mice with increased oxygen consumption in skeletal muscle tissue with as high as 246% of the wild type control mice. These mice weighed less and had lower levels of glucose and triglycerides and better. They were resistant to obesity (p.1115, abstract). Like wild type mice the mutant mice were capable of treadmill running at 145m/min for 15 minutes with no failures (p.118, co.2, 3rd

paragraph). These mice also had altered oxidative metabolic enzymes in the muscle tissue by promoting fatty acid oxidation to satisfy the respiratory demands of the mutant mice mitochondria (p.1119, 3rd paragraph). There were also tissue modifications in these mice with higher oxygen consumption, an unexpected increase in gonadal fat (p.1119, 2nd paragraph) and further indicate that skeletal muscle mimics some of the biochemical effects of exercise (p.119, 4th paragraph).

Thus it would have been obvious for one of ordinary skill in the art to incorporate the compositions of Titusville mutant hemoglobin as it is naturally modified (mutant) hemoglobin in a low oxygen affinity state and enhance oxygen consumption, increase oxidative metabolism, increase oxidative enzymatic activity, modify the tissues and enhance the exercise capacity of a subject. One of ordinary skill in the art would have been motivated to employ the erythrocyte free hemoglobin compositions with Titusville mutation in alpha subunit, as it lowers oxygen affinity of hemoglobin and enhances tissue oxygenation and oxidative metabolism, modify tissues and increase the exercise capacity of the subject. One of ordinary skill in the art would have reasonable expectation of success in making and using blood transfusion substitutes of pharmaceutical compositions comprising alpha globins with Titusville mutation for therapeutic enhancement of tissue oxygenation, oxidative metabolism, modification of tissues and for exercise capacity of the subject because of the teachings of Hoffman, and Li. Thus, the claimed invention was *prima facie* obvious.

Claim 11 is rejected under 35 USC 103 (a) as being unpatentable over Hoffman et al., (Patent No. US 5,028,588) as applied to claim 1 and 12 above in view of Abraham et al (Patent No. US 5,661,182) and further in view of De la Torre (Ann N Y Acad Sci.2002 Nov;977:196-215).

The above claims are directed to a pharmaceutical composition for treating or preventing cerebrovascular dementia by administering a subject alpha-gobin having the Titusville mutation.

Hoffman teaches pharmaceutical compositions of mutant hemoglobins that are useful as substitutes for red blood cells in delivery of oxygen to tissues (see entire

document) and a need for mutant hemoglobins with reduced affinity for oxygen (low oxygen affinity state; 'right-shifted') or increased P50, the partial pressure at which the oxygen-carrying solution is half saturated with oxygen, for efficient unloading of bound oxygen in tissues in need of O_2, a limitation observed with native hemoglobin, when used as a blood substitute (col. 1-2). Hoffman further teaches that one can use either certain naturally occurring mutants in α or β chain of the hemoglobin or use non-naturally occurring low affinity hemoglobin mutants (col.3-5, col.21-22 and table 1; col24, Table 2, col.27-28). He further **points out specifically a natural mutant where in Asp94Asn of α-globin (Titusville mutation**) as one of the preferred candidates that can used in the composition (col.7, lines 50-59, and teaches methods of making recombinant globin proteins (col.14-18) for mass production of compositions as blood substitutes (pharmaceutical composition). However, Hoffman does not teach treatment of conditions such as cerebrovascular dementia.

Abraham teaches effect of allosterically modifying hemoglobin towards a low oxygen affinity state sate in whole blood using modifying drug compounds. This is equivalent to having tiutsville mutation that brings down the affinity of hemoglobin for oxygen. This low oxygen affinity state, he observes, in vivo could be used in a wide variety of applications including in treatments for ischemia, heart disease, wound healing, some forms of **Alzheimers** (a form of cerebrovascular vascular dementia), depression, schizophrenia, adult respiratory distress syndrome etc..." (col.2, lines 33-43) that may be caused by low oxygen supply.

De la Torre teaches that there is now substantial evidence that sporadic alzheimers disease is a disorder of vascular disorder or **vascular dementia** (p.196, abstract). De la Torre provides epidemiologic evidence linking vascular factors for cerebrovascular pathology that can set in motion metabolic, neurodegenerative and cognitive changes in Alzheimers brain (p.197, 3rd & last paragraphs).

Thus it would have been obvious for one of ordinary skill in the art to incorporate the compositions of Titusville mutant hemoglobin as it is naturally modified (mutant) **hemoglobin in a low oxygen affinity state** and contemplate a method of treating conditions such as **cerebro vascular dementia** a form of Alzheimers disease. One of

ordinary skill in the art would have been motivated to employ the erythrocyte free hemoglobin compositions with Titusville mutation in alpha subunit, as it lowers oxygen affinity of hemoglobin and enhances tissue oxygenation, and contemplate on preventing or treating vascular dementia or Alzheimers. One of ordinary skill in the art would have reasonable expectation of success in making and using blood transfusion substitutes of pharmaceutical compositions comprising alpha globins with Titusville mutation for vascular dimentia therapy because of the teachings of Hoffman, Abraham and De la Torre as above.

Thus, the claimed invention was *prima facie* obvious.

Thus no claims are without prior art.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Dave Nguyen*, may be reached at **(571) 272-0731.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

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Patent Examiner
Art Unit 1633

SUMESH KAUSHAL
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